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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,126	03/14/2001	Torben Halkier	3631-0108P	6308

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	14

DATE MAILED: 05/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,126	HALKIER ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,8-12,17-24,28,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,8-12,17-24,28,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The amendment filed 7 April 2003 (Paper No. 13) has been entered in full. Claims 2, 4, 6-7, 13-16, 25-27, and 29-56 have been cancelled. Claims 1, 3, 5, 8-10, 12, 17, 19-24, and 28 have been amended. Claims 57 and 58 have been added. Claims 1, 3, 5, 8-12, 17-24, 28, and 57-58 are under examination.

2. The reference Fuller et al. (1998) has been received and considered on its merits as it pertains to the instant application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

4. The objection to claims **8-12, 17-24**, and **28** as set forth at pp. 4-5 ¶7 of the previous Office Action (Paper No. 12, 1 November 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 13, 7 April 2003).

5. The objections of claims **2, 4, 6, 7**, and **13-16** as set forth in the previous Office Action (Paper No. 12, 1 November 2002) are *moot* in view of Applicant canceling said claims (Paper No. 13, 7 April 2003).

6. The rejections of claims **1, 3, 5, 11-12, 18-19, 23**, and **24** under 35 USC §112 ¶2 as set forth at pp. 11 ¶17-18 in the previous Office Action (Paper No. 12, 1 November 2002) are *moot* in view of Applicant canceling said claims (Paper No. 13, 7 April 2003).

7. The rejections of claims **1, 22**, and **28** under 35 USC §112 ¶2 as set forth at pp. 11 ¶19-21 in the previous Office Action (Paper No. 12, 1 November 2002) are *moot* in view of Applicant canceling said claims (Paper No. 13, 7 April 2003).

8. The rejections of claims **2, 4, 6, 7,** and **13-16** under 35 USC §112 ¶ as set forth at pp. 5-10 ¶8-16 in the previous Office Action (Paper No. 12, 1 November 2002) are *moot* in view of Applicant canceling said claims (Paper No. 13, 7 April 2003).

Maintained Objections And/Or Rejections

9. Claims **1** and **12** are objected to because of the following informalities: these claims recite non-elected groups, specifically SEQ ID NO: 4, 6, and 35. Appropriate correction is required.

10. Claims **1, 3, 5, 8-12, 17-24, 28,** and **57-58** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons as set forth in at pp. 5-10 ¶8-16 of the previous Office Action (Paper No. 12, 1 November 2002). It is noted that Applicant added claims 57 and 58, but since the claims are within the scope of the previously examined claims they are included herein.

11. The Applicant traverses the 35 U.S.C. §112 ¶1 of claims 1, 3, 5, 8-12, 17-24, 28, and 57-58 as set forth in at pp. 5-10 ¶8-16 of the previous Office Action (Paper No. 12, 1 November 2002) on the grounds that: **(a)** peptide and polypeptide vaccination against self-proteins is well known in the art of immunology; antibodies raised against the self-protein will lead to its

destruction or interfere with its function and hence result in down regulation, **(b)** the specification provides ample guidance on how a skilled artisan can mutate SEQ ID NO: 2 and that the introduction of almost any mutation in SEQ ID NO: 2 will lead to an immunogenic variant or mutant capable of MHC II binding and result in breaking autotolerance (Applicant cites pp. 20-28 of the instant Specification); the function of any given OPGL or mutein thereof is nor relevant, **(c)** regulation and down-regulation are defined in the Specification and methods of synthesizing, screening, and evaluation non-peptide analogues would only require routine experimentation, **(d)** the OPGL polypeptide analogue must have the general formula included in claim 1 and therefore does not encompass any frameshift mutations; any mutation will result in a usable mutein for practicing the invention, and **(e)**. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

12. The Examiner maintains the rejection under 35 U.S.C. §112 ¶1 of claims 1, 3, 5, 8-12, 17-24, 28, and 57-58.

13. In regards to "**(a)**", it is not clear from the specification or the prior art that immunization with SEQ ID NO: 2 will lead to the desired effect. While the Examiner accepts the theory and practice of immunization against non-self or self as presented by the Applicant, the instant application is without evidence. However as taught by Bendayan (1995) "Possibilities of False Immunocytochemical Results Generated by the Use of Monoclonal Antibodies: The Example of the Anti-proinsulin Antibody." The Journal of Histochemistry and Cytochemistry **43**(9): 881-886 antibodies raised against a specific sequence are not only specific for the parent protein but can display unwanted cross-reactivity with related and unrelated proteins (pp. 886). Thus it is entirely possible that if the constructs are used to the full scope of the claims as written, the

invention may trigger rampant and non-specific breaking of autotolerance resulting in an autoimmune disease. Thus without guidance or examples, the level of uncertainty is daunting and thus impedes a reasonable expectation of success to use the claimed invention.

14. Concerning **"(b)"**, while the Examiner accepts that the introduction of mutations into SEQ ID NO: 2 is possible, this does not guarantee that the mutation will yield a useful variant to practice the invention. Jobling and Holmes (1991) "Analysis of structure and function of the B subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-1767 teaches that a single point mutation can destroy the antigenicity of a protein (pp. 1763-1764). In regards to polypeptides, such as SEQ ID NO: 2, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to

change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active or immunogenic muteins, this is not adequate guidance as to the nature of active or immunogenic derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy antigenicity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1): 34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Furthermore on "**(b)**", breaking autotolerance can have the unintended result of triggering an autoimmune reaction due to unwarranted cross-reactivity. Bendayan (1995) "Possibilities of False Immunocytochemical Results Generated by the Use of Monoclonal Antibodies: The Example of the Anti-proinsulin Antibody." The Journal of Histochemistry and Cytochemistry **43**(9): 881-886 teaches that antibodies raised against a specific sequence can not only be specific for the parent protein but display unwanted cross-reactivity with related and unrelated proteins (pp. 886). Thus it is entirely possible that if the constructs are used to the full scope of the claims as written, the invention may trigger rampant and non-specific breaking of autotolerance resulting in an autoimmune disease.

16. On **"(c)"**, the Examiner accepts the Applicant's definition of regulation. The Examiner maintains, however, that "analogue" still remains an ill-defined concept. Further, the synthesizing, screening, and evaluation of non-peptide analogues may be routine but has a level of unpredictability for the action of any given analogue of SEQ ID NO: 2 an unknown activity *in vitro* and *in vivo*, and thus requires undue experimentation to characterize.

17. In response to **"(d)"** as discussed above, the general formula of claim 1 encompasses non-elected matter. In addition, as discussed above, the synthesis, screening, and evaluation of muteins of SEQ ID NO: 2 presents an undue burden of experimentation on the skilled artisan with a level of unpredictability. Also noted above, the immunogenecity of any given mutein of SEQ ID NO: 2 is not guaranteed and must be evaluated with the caveat of possibly triggering an autoimmune reaction beyond what is desired. Li et al. (June 1980) "β-Endorphin omission analogs: Dissociation of immunoreactivity from other biological activities." Proc. Natl. Acad. Sci. USA 77(6): 3211-3214 teaches that analogues of human β-endorphin with the deletion of a

single residue may retain activity but loose immunoreactivity and visa verse (Table 1-5). Therefore a degree of uncertainty exists on whether or not OPGL and its analogues will share immunoreactivity and activity or neither. Thus the skilled artisan is confronted with a burden of experimentation and contradictory guidance from the prior art to practice the invention using the OPGL analogues as claimed.

18. On **"(e)"**, the Examiner maintains that any immune response produced by SEQ ID NO: 2 or other muteins is not assured of accomplishing the objective set forth in the preamble of claim 1. Münch and Robinson (2002) "Potential neurotoxic inflammatory responses to Aβ vaccination in humans." J. Neural. Transm. **109**: 1081-1087 teaches that the use of endogenous Aβ epitopes to trigger an immune response in Alzheimer's patients lead to unintended triggering of an autoimmune response. During the clinical trials, 15 of the 360 patients suffered central nervous system inflammation and 2 suffered ischemic strokes (pp. 1081-1082). In addition, Münch and Robinson (2002) caution that the subsequent autoimmune reactions may be long lasting and irreversible (pp. 1085). Further, the autoimmune tolerance that was broken in the human patients failed to result in the removal or clearance of the Aβ containing plaques (pp. 1084). A large and burdensome amount of experimentation, fraught with uncertainty, and accomplished only through successive trial and error exists to practice the invention. Therefore, absent any examples, evidence, or concrete guidance, the skilled artisan is not given sufficient guidance to use the invention as claimed. Also, the biological relevance, and physiological significance of the muteins of SEQ ID NO: 2 are unknown, adding another layer of complication to practice the invention.

19. Therefore the rejection of claims 1, 3, 5, 8-12, 17-24, 28, and 57-58 under 35 U.S.C. §112 ¶1 is hereby maintained.

Summary

20. No claims are allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher J. Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
April 24, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER